FORM PTO-1390 (Modified) (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

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INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US98/18953	11 SEPT 1998	11 SEPT 1997

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TITLE OF INVENTION

INTRANASAL FORMULATION CONTAINING SCOPOLAMINE AND METHOD OF TREATING MOTION SICKNESS

APPLICANT(S) FOR DO/EO/US

ACHARI, Raja G.; BEHL, Charanjit R.; CHOWHAN, Prafulla K.; DE MEIRELES, C. Jorge; DUA, Ramneik; ROMEO, Vincent D.; SILENO, Anthony P.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☒ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

- Letter of Clarification regarding submission of a copy of declaration.

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/486839	PCT/US98/18953	719-75 PCT/US

21. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO **$970.00**	
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO **$840.00**	
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$690.00**	
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$670.00**	
☒	International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$96.00**	
	ENTER APPROPRIATE BASIC FEE AMOUNT =	**$96.00**
	Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	21 - 20 =	1	x $18.00	**$18.00**
Independent claims	3 - 3 =	0	x $78.00	**$0.00**
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**
	TOTAL OF ABOVE CALCULATIONS =			**$114.00**
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable)**. ☐				**$0.00**
	SUBTOTAL =			**$114.00**
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				**$0.00**
	TOTAL NATIONAL FEE =			**$114.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☒				**$40.00**
	TOTAL FEES ENCLOSED =			**$154.00**

Amount to be: refunded	$
charged	$

☒ A check in the amount of **$154.00** to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. in the amount of to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **08-2461** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

KIRK M. MILES, ESQ.
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NEW YORI 11791
(973) 331-1700

SIGNATURE

KIRK M. MILES, ESQ.
NAME

37,891
REGISTRATION NUMBER

MARCH 1, 2000
DATE

INTRANASAL FORMULATION CONTAINING SCOPOLAMINE AND METHOD OF TREATING MOTION SICKNESS

CROSS-REFERENCE TO RELATED APPLICATION

The present application claims priority to co-owned U.S. Provisional Application Serial No. 60/058,651 filed on 11 September 1997, the entire contents of which is hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to pharmaceutical formulations containing scopolamine. More particularly, the present invention relates to nasal gel formulations for intranasal delivery of scopolamine, in particular, for preventing and/or treating motion sickness.

BACKGROUND OF THE INVENTION

Scopolamine, and more particularly, its salt Scopolamine Hydrobromide, have been investigated for a variety of clinical indications. Examples of potential uses for scopolamine include the treatment of general nausea and/or vomiting, motion sickness, peripheral vertigo, post operative conditions and the use as an anesthetic.

Several delivery routes have been utilized for administering scopolamine. These include oral, transdermal, buccal and intranasal administration. Oral and transdermal administration, however, do not provide a rapid onset of a therapeutically effective amount of scopolamine as determined by bioavailability studies. Oral administration of scopolamine is further complicated by first-pass metabolism in the liver which can significantly reduce

its bioavailability. Buccal administration of scopolamine has also been investigated. It has been reported, however, that the bioavailability from buccal administration does not significantly differ from oral administration.

Intranasal delivery of scopolamine has shown potential for the rapid onset of a therapeutically effective amount of the compound. For example, International Application No. PCT/US82/00941, published as WO 83/00286 on February 3, 1983 discloses treatment of sudden motion sickness with a nasal spray of scopolamine. While this reference discusses the rapid onset of scopolamine via the intranasal delivery route, there is no consideration of sustained delivery of scopolamine over a period of time or the storage stability of such a formulation.

While intranasal administration of various drugs such as scopolamine is known, the development of intranasal formulations to provide a therapeutically effective amount of a drug and the stability of the formulation over time is often unpredictable. While many drugs can be provided in intranasal formulations, the drug delivery offered by such formulations cannot be readily predicted and can dramatically differ between apparently similar formulations. Moreover, for an intranasal formulation of scopolamine to be effective in the prevention and treatment of acute conditions such as motion sickness, the ability to provide a therapeutically effective amount within 30 minutes, and desirably within 20 minutes, of administration is necessary. Likewise, considerations such as providing a therapeutically effective amount of the drug as soon as possible, maintaining a therapeutically effective level over a sustained amount of time and stability of the formulation over time must be balanced.

In considering the intranasal delivery of drugs, the pharmokinetics thereof are often considered. For example, ionization of a drug is believed to directly influence membrane penetration of the drug, and therefore, the absorption potential of the drug into the blood

stream. In particular, the ionization of a drug and therefore its absorption potential, is largely determined by the drug's dissociation constant, pK_a, as well as the pH of the solution in which the drug is dissolved. As reported by Mayersohn in Modern Pharmaceutics, Banker & Rhodes, 1979, Ch. 2, Pg. 40, basic compounds are best absorbed from alkaline solutions where $pH > pK_a$. Thus, it is generally believed that formulations for delivering basic drugs, in particular intranasal formulations, are best absorbed into the bloodstream when the basic drug is prepared in a formulation solution having a pH above the dissociation constant of the drug.

For example, scopolamine is known to be a basic drug. In order to provide effective membrane penetration and absorption through intranasal delivery, heretofor it has been understood that scopolamine hydrobromide should be formulated in a basic solution having a formulation pH greater than 7.6.

Intranasal formulations of scopolamine hydrobromide at pH levels below 7 have been investigated. For example, in "Absorption for Nasal Mucous Membrane: Systemic Effect of Hyoscine Following Intranasal Administration" by Tonndorf et al. in Ann. Oto. Rhino. Laryngol., vol. 62, 630, 1953, intranasal scopolamine spray formulations were prepared at a pH between 5.7-6.0. Moreover, U.S. Patent Application Serial No. 07/765,615 entitled "Intranasal Scopolamine Preparation and Method" discloses scopolamine formulations for intranasal spray delivery prepared at a pH of 4 ± 0.2. Both of these references disclose formulations which are inherently inefficient requiring 0.65 mg/ml and 0.4 mg/ml of scopolamine per dose, respectively. Such high dosages are wasteful of drug, add unnecessary cost to consumer and may cause undesirable side effects.

Accordingly, there is a need in the art for intranasal formulations that provide a therapeutically effective amount of scopolamine into the bloodstream within a relatively

short time period (e.g., 30 minutes or less), that provide therapeutically effective levels of scopolamine for a sustained amount of time, that do not degrade over time and are not irritating to the nasal cavity.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide an intranasal formulation for preventing and/or treating nausea and/or vomiting and other symptoms associated with motion sickness.

It is a further object of the invention to provide a scopolamine nasal formulation capable of prolonged shelf storage.

It is a further object of the invention to provide an intranasal formulation capable of achieving rapid plasma concentrations without achieving dangerous peak plasma concentrations.

In the efficient attainment of these and other objects, the present invention provides an intranasal formulation including scopolamine in a pharmaceutically acceptable carrier. The formulation has a pH below about 4.0, desirably at or below about 3.5, and a salt concentration below about 200 mM, desirably at or below 100 mM, such as for example at or below 50 mM. Desirably, the formulation incorporates polyvinyl alcohol therein. Preferably the carrier is provided as an intranasal gel, with the polyvinyl alcohol acting as a gelling agent for the composition. The scopolamine is preferably provided as a pharmaceutically acceptable salt, such as for example, scopolamine hydrobromide.

The present invention also relates to a method of preventing and/or treating nausea including administering intranasally to a mammal an effective amount of scopolamine, chemically modified equivalents and pharmaceutical salts thereof in a pharmaceutically acceptable carrier at a pH below about 4.0 and a salt concentration below about 200 mM, with the carrier incorporating polyvinyl alcohol.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph representing average plasma concentration over time of intranasal gel formulations incorporating different gelling agents.

Figure 2 is a graph representing product degradation as a function of the percentage formulation molarity over time for intranasal gel formulations.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is an intranasal formulation for delivery of scopolamine. As used herein, "intranasal formulation" is intended to include a pharmaceutically acceptable carrier which incorporates the active agent, i.e., scopolamine. For purposes of the present invention, "pharmaceutical carrier" includes nasal sprays, nasal drops, gels, ointments, creams and the like. The present formulations may be administered using, for example, a nasal tampon or a nasal sponge containing the present formulation. Desirably, however, scopolamine is delivered in a gel formulation as set forth in more detail below.

Polyvinyl alcohol (PVA) is known to enhance viscosity. It is well known that PVA should be used in a pH range of about 5 - 8. Thus, one skilled in the art would not be motivated to formulate PVA-containing pharmaceutical compositions at a pH lower than 5

and would reject such a composition as a pharmaceutical carrier for, e.g., scopolamine. Surprisingly, it has been demonstrated in the present invention that gel formulations of scopolamine having PVA as the main gelling agent provide products with excellent stability which are superior to prior art spray formulations, as well as gel formulations using methyl cellulose. Thus, nasal gel preparations of scopolamine according to the present invention are prepared using PVA. The amount of PVA that can be used in the present invention can vary depending upon the specific formulation. In particular, the amount of PVA contained in the present invention is that amount which is sufficient to form a pharmaceutically acceptable gel. Desirably, PVA is present in the present formulations up to about 30%, more desirably, up to about 20%, such as for example up to about 10%.

Gel systems having as a main component a composition having similar properties to PVA and which provide results substantially as set forth in the Examples below are also contemplated by the present invention. For example, gelling agents including the following can be used as a substitute for or in addition to PVA: alginates, gums, starches, polyacrylates, dextrans, chitosans and mixtures thereof.

In the present invention, scopolamine is combined with the pharmaceutical carrier at a pH of about 4. Desirably, scopolamine is combined with the pharmaceutical carrier at or below about pH 3.5.

In addition to maintaining the pH of the present formulation at or below 4, the salt concentration thereof must be maintained at or below about 200 mM. Desirably, the salt concentration is maintained at or below about 100 mM, such as for example at or below about 50 mM.

For purposes of the present invention, the term "scopolamine" as used herein is intended to include those pharmaceutically active scopolamine compositions set forth in The

Merck Index (11th Edition on page 8363) including [7(S)-(1α,2β,4β,5α,7β)]-α-(Hydroxymethyl)benzeneacetic acid 9-methyl-3-oxa-9-azatricyclo-[3.3.$0^{2,4}$]non-7-yl ester and 6β,7β-epoxy-1αH,5αH-tropan-3α-ol (-)-tropate. Moreover, as used herein, "scopolamine" also includes pharmaceutical salts and hydrated forms, as well as all chemically modified equivalents thereof. Scopolamine hydrobromide or scopolammonium bromide ($C_{17}H_{22}BrNO_4 \cdot 3H_2O$), scopolamine hydrochloride ($C_{17}H_{22}ClNO_4$), methscopolamine bromide and methscopolamine nitrate ($C_{18}H_{24}N_2O_7$) are examples of pharmaceutical salts which can be used in accordance with the present invention. As used herein, "chemically modified equivalents" is intended to include compositions which may have a chemical structure that differs from scopolamine but which functions in a similar manner in the body, such as for example prodrugs, analogs, biologically active fragments and the like.

Such compositions have clinical utility to prevent and treat nausea and/or vomiting associated with, for example motion sickness. In addition, such compositions can be used as a sedative and as a pre-anesthetic. The present formulations, thus can be used to treat and/or prevent a variety of symptoms.

As set forth above, the present formulations can be used to both prevent and treat nausea and/or vomiting induced by motion sickness. Thus, the present formulations can be administered to a mammal prior to any symptoms associated with motion sickness and can prevent nausea and/or vomiting which are often symptoms thereof. Moreover, once onset of motion sickness symptoms has occurred in a patient, the present formulations can be administered to the patient and will provide alleviation or substantial decrease of the nausea and/or vomiting associated with motion sickness.

In the present invention, many other excipients, known from the pharmaceutical literature, may be added to the formulations, such as preservatives, surfactants, co-solvents,

adhesives, antioxidants, buffers, viscosity enhancing agents and agents to adjust the pH or the osmolarity.

The various forms of the intranasal formulations set forth above can optionally include a buffer to maintain the pH of the scopolamine formulation, a pharmaceutically acceptable thickening agent, humectant and surfactant. Desirably, the pH of the buffer is selected to maintain the stability of scopolamine. In particular, the pH of the buffer is selected to optimize the stability of the scopolamine in the present inventive formulations. As set forth previously, the pH of the buffer is desirably below about 4, more desirably at or below about 3.5. Buffers that are suitable for use in the present invention include, for example, hydrochloride, acetate, citrate, carbonate and phosphate buffers.

The viscosity of the compositions of the present invention can be maintained at a desired level using a pharmaceutically acceptable thickening agent. Thickening agents that can be used in accordance with the present invention include for example, xanthan gum, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and mixtures thereof. The concentration of the thickening agent will depend upon the agent selected and the viscosity desired.

The compositions of the present invention also include a tolerance enhancer to reduce or prevent drying of the mucus membrane and to prevent irritation thereof. Suitable tolerance enhancers that can be used in the present invention include, for example, humectants, sorbitol, propylene glycol, mineral oil, vegetable oil and glycerol; soothing agents, membrane conditioners, sweeteners and mixtures thereof. The concentration of the tolerance enhancer(s) in the present compositions will also vary with the agent selected.

In order to enhance absorption of the scopolamine through the nasal mucosa, a

therapeutically acceptable surfactant may be added to the intranasal formulation. Suitable surfactants that can be used in accordance with the present invention include, for example, polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides, such as for example, Tween 80, Polyoxyl 40 Stearate, Polyoxy ethylene 50 Stearate, fusidates, bile salts and Octoxynol. Suitable surfactants include non-ionic, anionic and cationic surfactants. These surfactants can be present in the intranasal formulation in a concentration ranging from about 0.001% to about 20% by weight.

In the present invention other optional ingredients may also be incorporated into the nasal delivery system provided they do not interfere with the action of the scopolamine or significantly decrease the absorption of scopolamine across the nasal mucosa. Such ingredients can include, for example, pharmaceutically acceptable excipients and preservatives. The excipients that can be used in accordance with the present invention include, for example, bio-adhesives and/or swelling/thickening agents.

In the present invention, any other suitable absorption enhancers as known in the art may also be used.

Preservatives can also be added to the present compositions. Suitable preservatives that can be used with the present compositions include, for example, benzyl alcohol, parabens, thimerosal, chlorobutanol and benzalkonium, with benzalkonium chloride being preferred. Typically, the preservative will be present in the present compositions in a concentration of up to about 2% by weight. The exact concentration of the preservative, however, will vary depending upon the intended use and can be easily ascertained by one skilled in the art.

Another embodiment of the present invention is an intranasal formulation for

preventing or treating motion sickness. This formulation includes scopolamine hydrobromide in a PVA gel solution at a pH at or below about 3.5 and a salt concentration below about 100 mM. In this embodiment, the PVA gel solution can include mixtures of other gelling agents or bio-adhesives, such as for example, alginates, gums, starches, polyacrylates, dextrans, chitosans and mixtures thereof. Moreover, the PVA gelling agent can be replaced with other similar gelling/bio-adhesives provided that such agents produce the surprising results as set forth in the examples of the present invention.

Another embodiment of the present invention is a method of preventing and/or treating nausea and/or vomiting. This method includes administering intranasally to a mammal an effective amount of scopolamine, chemically modified equivalents and pharmaceutical salts thereof in a pharmaceutically acceptable carrier at a pH at or below about 4.0 with a salt concentration at or below about 200 mM. The pharmaceutically acceptable carrier is desirably PVA, however, other gelling/bio-adhesives which provide results similar to those set forth in the present experimental examples are also contemplated. Examples of such gelling/bio-adhesives include, alginates, gums, starches, polyacrylates, dextrans, chitosans and mixtures thereof. Moreover, the pharmaceutically acceptable carrier can include PVA and mixtures of other appropriate gelling/bio-adhesives provided the formulation produces superior pharmacokinetic profiles along the lines set forth in the Examples.

The pharmaceutically acceptable carrier of the present invention is specifically designed for intranasal administration. Such formulations are safe and effective for intranasal delivery to mammals, including humans. Formulations of such carriers are well known in the art and specific examples thereof are provided below.

In the present embodiment of the invention, the salt concentration is desirably at or

below 100 mM, such as for example, 50 mM. As set forth above, the pH of the present formulation is desirably at or below about 3.5.

The following examples are set forth to illustrate the formulations of the present invention, as well as the surprising results achieved therewith. These examples are provided for purposes of illustration only and are not intended to be limiting in any sense.

EXAMPLE 1

Inventive and Comparative Formulations

Example 1 sets forth a comparative intranasal scopolamine hydrobromide nasal gel formulation containing methyl cellulose with a buffer concentration of 25 mM (Formulation 1) and three inventive intranasal scopolamine hydrobromide nasal gel formulations according to the present invention containing PVA at 20, 50 and 100 mM buffer concentrations (Formulations 2, 3 and 4, respectively).

Nasal gel Formulation 1 containing a methyl cellulose gelling agent at a pH of about 3.5 and having a scopolamine concentration of about 0.2 mg/0.1gm at a buffer concentration of 0.025M (25 mM) was prepared as follows:

Formulation 1 - Methyl Cellulose (25 mM)

Composition	**Quantity - 100mL(Gm)**
Scopolamine Hydrobromide, USP	0.20
Citric Acid Anhydrous, USP	0.37
Sodium Citrate Dihydrate, USP	0.17
Sodium Metabisulfite, NF	0.1
Glycerine (96%), USP	5.0
Methyl cellulose (4000 cps), USP	2.0
Benzalkonium Chloride (50%), NF	0.04
Purified Water, USP	100 Q.S.

Nasal gel Formulation 2 containing a PVA gelling agent at a pH of about 3.5 and having a scopolamine concentration of about 0.2 mg/0.1gm at a buffer concentration of 0.02M (20 mM) was prepared as follows:

Formulation 2 - PVA (20 mM)

Composition	Quantity - 100mL(Gm)
Scopolamine Hydrobromide, USP	0.20
Citric Acid Anhydrous, USP	0.32
Sodium Citrate Dihydrate, USP	0.098
Sodium Metabisulfite, NF	0.1
Glycerine (96%), USP	5.0
Polyvinyl Alcohol, USP	10.0
Benzalkonium Chloride (50%), NF	0.04
Purified Water, USP	100 Q.S.

Formulation 3 - PVA (50 mM)

Composition	Quantity - 100mL(Gm)
Scopolamine Hydrobromide, USP	0.20
Citric Acid Anhydrous, USP	0.73
Sodium Citrate Dihydrate, USP	0.34
Sodium Metabisulfite, NF	0.1
Glycerine (96%), USP	5.0
Polyvinyl Alcohol, USP	10.0
Benzalkonium Chloride (50%), NF	0.04
Purified Water, USP	100 Q.S.

Formulation 4 - PVA (100 mM)

Composition	Quantity - 100mL(Gm)
Scopolamine Hydrobromide, USP	0.20
Citric Acid Anhydrous, USP	1.42
Sodium Citrate Dihydrate, USP	0.76
Sodium Metabisulfite, NF	0.1
Glycerine (96%), USP	5.0
Polyvinyl Alcohol, USP	10.0
Benzalkonium Chloride (50%), NF	0.04
Purified Water, USP	100 Q.S.

EXAMPLE 2

Comparison of Methyl Cellulose vs. PVA Formulations: Scopolamine Absorption

Example 2 is a comparison of scopolamine absorption into the blood stream from Formulation 1 (methyl cellulose at 25 mM buffer concentration) vs. Formulation 2 (PVA at 20 mM buffer concentration). Nasal gel formulations were prepared based on Formulations 1-2 set forth above. These Formulations were adjusted to a pH value of about 3.5 with citric acid solution or sodium citrate solution as needed.

The nasal gel Formulations 1 and 2 were administered intranasally to 10 healthy humans. The plasma concentration of scopolamine free base was measured in these individuals over time for a period of 240 minutes by LC/MS/MS. The average results of these measurements are shown in Table 1, and depicted in Figure 1.

Table 1

Comparison of Methyl Cellulose vs. PVA Formulations: Scopolamine Absorption

Time (minutes)	Formulation 1#	Formulation 2#
0	0 ± 0	0 ± 0
5	28.4 ± 45.1	80.7 ± 58.3
10	106 ± 157	138.6 ± 86.7
20	136 ± 144	203 ± 124
30	144 ± 100	219 ± 112
45	152 ± 119	220 ± 111
60	137 ± 106	188 ± 127
120	119 ± 99.0	123 ± 81.8
240	44.1 ± 37.5	58.3 ± 39.7
C_{max}* (pg/ml)	204 ± 161	248 ± 123
T_{max}* (minutes)	45.5 ± 31.2	35.5 ± 12.8

#Average Plasma Concentration of Scopolamine Free Base (pg/ml).

* C_{max} and T_{max} values represent an average of the respective C_{max} and T_{max} values obtained for each patient.

As can be seen from these results, absorption of scopolamine into the blood was within acceptable limits as recognized by those skilled in the art for both Formulations 1 and 2.

A comparison of the plasma concentrations of scopolamine free base for Formulation 1 (methyl cellulose) with Formulation 2 (PVA) demonstrates the unexpected and surprising results achieved through the present invention. As is clearly evident from Figure 1 which is a graphic representation of the data set forth in Table 1, the average plasma concentration over time of Formulation 1 (methyl cellulose) was considerably below that of Formulation 2 (PVA). Thus, the intranasal formulation according to the

present invention (Formulation 2) achieves significantly higher scopolamine absorption into the blood compared to intranasal Formulation 1 (methyl cellulose). Additionally, rapid onset of the drug is achieved with the present inventive formulation (Formulation 2), as is evidenced by the graph which shows scopolamine free base concentrations of Formulation 2 which according to the present invention more than doubled that of the Formulation 1 in 5 minutes.

EXAMPLE 3

Comparison of Stability of PVA and Methyl Cellulose Intranasal Formulations

This Example provides stability data comparing Formulation 1 (methyl cellulose) with Formulation 2 (PVA) at various temperatures and relative humidities.

For purposes of the present examples, formulations having unacceptable stability exhibited more than 1% degradation of product resulting in the formation of tropic acid over 6 months of storage at 40°C and 75% humidity in accordance with generally accepted FDA guidelines for minimum stability.

Nasal gel Formulations 1 and 2 having a scopolamine concentration of 0.2 mg/0.1gm at a buffer concentration of 0.025M (25mM) and 0.02 (20 mM), respectively were prepared in accordance with the formulations of Example 1.

A. Stability at 40°C/75% RH

Formulations 1 and 2 were adjusted to a pH value of about 3.5 with citric acid solution or sodium citrate solution as needed. The respective formulations were stored in a standard drug container in both upright and inverted positions at a temperature of 40° C and 75 % relative humidity, over time for a period of 6 months. Various measurements were taken to represent stability of each formulation, including Scopolamine HBr content

as a percentage, degradation of the product represented by the percentage of tropic acid appearing in the formulation and viscosity. The results are set forth in Table 2 (Formulation 1 - methyl cellulose) and Table 3 (Formulation 2 - PVA) below.

Table 2

Methyl Cellulose (25 mM)

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.48	102.6	not detectable	4393
1	Upright	3.30	101.0	not quantifiable	1452
1	Inverted	3.31	101.7	not quantifiable	1341
2	Upright	3.13	102.3	not quantifiable	--
2	Inverted	3.13	104.1	not quantifiable	--
3	Upright	3.11	106.6	0.23	--
3	Inverted	3.09	104.2	0.23	--
6	Upright	3.03	101.4	0.45	206
6	Inverted	3.08	102.3	0.45	259

Table 3

PVA (20 mM)

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.64	104.0	not detectable	1711
1	Upright	3.52	100.9	not quantifiable	1714
1	Inverted	3.50	100.8	not quantifiable	1761
2	Upright	3.49	100.8	not quantifiable	--
2	Inverted	3.46	101.0	not quantifiable	--
3	Upright	3.31	102.8	0.21	--
3	Inverted	3.29	103.5	0.22	--
4	Upright	3.09	102.0	0.27	--
4	Inverted	3.11	103.0	0.27	--
5	Upright	3.08	102.7	0.33	--
5	Inverted	3.06	102.9	0.34	--
6	Upright	3.03	105.4	0.50	1564
6	Inverted	3.03	102.6	0.40	1618

As is evident from the data depicted in Table 2, Formulation 1 (methyl cellulose) provides stability with respect to scopolamine HBr content, maintaining 101.4% and 102.3 % for upright and inverted containers, respectively, over 6 months storage. Moreover, the degradation of this gel formulation over time is within acceptable limits, demonstrated by 0.45 percent of tropic acid in the formulation after 6 months. The viscosity of Formulation 1 (methyl cellulose), however, rapidly decreased from an initial level of 4393 cts to 1452 cts and 1341 cts for upright and inverted containers, respectively, after only 1 month of storage, and further decreasing to 206 cts and 209 cts for upright and inverted containers, respectively, after 6 months storage, demonstrating an unacceptable change in viscosity for stability.

As is evident from the data depicted in Table 3, Formulation 2 (PVA) remains both chemically and physically stable over the entire 6 month period, as evidenced by the Scopolamine HBr content, degradation product and viscosity of the formulation remaining within acceptable ranges, even after 6 months of storage time.

B. Stability at 30°C/60% RH

The stability of Formulations 1 and 2 was investigated at a temperature of 30°C at 60% relative humidity over the course of 6 months substantially as set forth above. The data from this investigation is set forth below in Table 4 (Formulation 1 - methyl cellulose) and Table 5 (Formulation 2 -PVA):

Table 4

Methyl Cellulose (25 mM)

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.48	102.6	not detectable	4393
1	Upright	3.40	102.3	not detectable	-
1	Inverted	3.42	102.7	not detectable	-
2	Upright	3.28	104.6	not detectable	-
2	Inverted	3.26	104.0	not detectable	-
3	Upright	3.26	106.9	not quantifiable	2082
3	Inverted	3.24	107.5	not quantifiable	2233
6	Upright	3.15	103.4	not quantifiable	1083
6	Inverted	3.16	103.2	not quantifiable	1305

Table 5

PVA (20 mM)

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.64	104.0	not detectable	1711
1	Upright	3.60	101.5	not detectable	--
1	Inverted	3.59	100.5	not detectable	--
2	Upright	3.63	100.7	not detectable	--
2	Inverted	3.66	101.7	not detectable	--
3	Upright	3.51	104.7	not quantifiable	1665
3	Inverted	3.52	104.3	not quantifiable	1637
6	Upright	3.34	105.4	not quantifiable	1633
6	Inverted	3.40	104.2	not quantifiable	1595

As is evident from the data depicted in Table 4, Formulation 1 (methyl cellulose) stored at 30° C and 60% relative humidity provides stability with respect to scopolamine HBr content, maintaining 103.4% and 103.2 % for upright and inverted containers, respectively, over 6 months storage. Moreover, the degradation of this gel formulation over time is within acceptable limits, demonstrated by no quantifiable percent of tropic acid in the formulation after 6 months. The viscosity of Formulation 1, however, again rapidly decreased from an initial level of 4393 cts to 2082 cts and 2233 cts for upright and inverted containers, respectively, after 3 months of storage, and further decreased to 1083 cts and 1305 cts for upright and inverted containers, respectively, after 6 months storage, demonstrating an unacceptable change in viscosity for stability.

As is evident from the data depicted in Table 5, Formulation 2 (PVA) remains both chemically and physically stable over the entire 6 month period, as evidenced by the Scopolamine HBr content, degradation product and viscosity of the formulation remaining within acceptable ranges, even after 6 months of storage time.

C. Stability at 25°C/60% RH

The stability of Formulations 1 and 2 was investigated at a temperature of 25°C at 60% relative humidity over the course of 6 months substantially as set forth above. The data from this investigation is set forth below in Table 6 (Formulation 1 - methyl cellulose) and Table 7 (Formulation 2 -PVA):

Table 6

Methyl Cellulose (25 mM)

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.48	102.6	not detectable	4393
3	Upright	3.26	107.0	not detectable	--
3	Inverted	3.32	102.4	not detectable	--
6	Upright	3.19	103.2	not quantifiable	1755
6	Inverted	3.19	103.2	not quantifiable	2129

Table 7

PVA (20 mM)

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.64	104.0	not detectable	1711
3	Upright	3.55	104.4	not detectable	--
3	Inverted	3.56	103.8	not detectable	--
6	Upright	3.46	104.0	not quantifiable	1640
6	Inverted	3.47	104.6	not quantifiable	1640

As is evident from the data depicted in Table 6, Formulation 1 (methyl cellulose)

provides stability with respect to scopolamine HBr content, maintaining 103.2 % for both the upright and inverted containers over 6 months storage. Moreover, the degradation of this gel formulation over time is within acceptable limits, demonstrated by no quantifiable percent of tropic acid in the formulation after 6 months. The viscosity of Formulation 1 (methyl cellulose), however, again decreased from an initial level of 4393 cts to 1755 cts and 2129 cts for upright and inverted containers, respectively, after 6 months storage, demonstrating an unacceptable change in viscosity for stability.

As is evident from the data depicted in Table 7, Formulation 2 (PVA) remains both chemically and physically stable over the entire 6 month period, as evidenced by the Scopolamine HBr content, degradation product and viscosity of the formulation remaining within acceptable ranges, even after 6 months of storage time.

D. Stability at 15°C/40% RH

The stability of Formulations 1 and 2 was investigated at a temperature of 15°C at 40% relative humidity over the course of 6 months substantially as set forth above. The data from this investigation is set forth below in Table 8 (Formulation 1 - methyl cellulose) and Table 9 (Formulation 2 -PVA):

Table 8

Methyl Cellulose (25 mM)

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.48	102.6	not detectable	4393
3	Upright	3.35	106.5	not detectable	--
3	Inverted	3.33	105.9	not detectable	--
6	Upright	3.30	105.6	not detectable	3418
6	Inverted	3.33	103.7	not detectable	3220

Table 9

PVA (20 mM)

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.64	104.0	not detectable	1711
3	Upright	3.62	103.2	not detectable	--
3	Inverted	3.62	103.4	not detectable	--
6	Upright	3.56	104.2	not detectable	1709
6	Inverted	3.55	104.1	not detectable	1839

As is evident from the data depicted in Table 8, even with Formulation 1 (methyl cellulose) stored at 15° C and 40% relative humidity, stability with respect the viscosity of the formulation decreased from an initial level of 4393 cts to 3418 cts and 3220 cts for upright and inverted containers, respectively, after 6 months storage. Thus, even under cold storage conditions, the stability of Formulation 1 (methyl cellulose) was inadequate, as demonstrated by an unacceptable change in viscosity.

As is evident from the data depicted in Table 9, Formulation 2 (PVA) remains both chemically and physically stable over the entire 6 month period, as evidenced by the Scopolamine HBr content, degradation product and viscosity of the formulation remaining within acceptable ranges, even after 6 months of storage time.

Thus, these data support the surprising conclusion that Formulation 2 containing PVA as a gelling agent is consistently more stable compared to Formulation 1 containing methyl cellulose as a gelling agent over the entire 6 month investigational period at a variety of temperatures and relative humidities.

EXAMPLE 4

Effect of Molarity on Stability of PVA Formulations (20 mM, 50 mM and 100 mM)

Example 4 is a study of the effect of different molarities on PVA stability over time. In particular, Formulations 2, 3 and 4 were prepared substantially as set forth in Example 1 with molarities of 20 mM, 50 mM and 100 mM, respectively.

Formulations 2, 3 and 4 were adjusted to a pH value of about 3.5 with citric acid solution or sodium citrate solution as needed. The respective formulations were stored in a standard drug container in both upright and inverted positions at various temperatures and relative humidity, over time for a period of 6 months. Various measurements were taken to represent stability of each formulation, including Scopolamine HBr content as a percentage, degradation of the product represented by the percentage of tropic acid appearing in the formulation and viscosity. The results are set forth in Tables 10 - 21 below.

Table 10

Formulation 2 at 40°C/75% Relative Humidity (%RH)

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.64	104.0	not detectable	1711
1	Upright	3.52	100.8	not quantifiable	1714
1	Inverted	3.50	100.8	not quantifiable	1761
2	Upright	3.49	100.8	not quantifiable	--
2	Inverted	3.46	101.0	not quantifiable	--
3	Upright	3.31	102.8	0.21	--
3	Inverted	3.29	103.5	0.22	--
4	Upright	3.09	102.0	0.27	--
4	Inverted	3.11	103.0	0.27	--
5	Upright	3.08	102.7	0.33	--
5	Inverted	3.06	102.9	0.34	--
6	Upright	3.03	105.4	0.50	1564
6	Inverted	3.03	102.6	0.40	1618

Table 11

Formulation 3 at 40°C/75% RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.50	103.1	not detectable	1705
1	Upright	3.50	104.5	not quantifiable	1659
1	Inverted	3.40	102.2	not quantifiable	1696
2	Upright	3.40	102.5	0.22	--
2	Inverted	3.40	103.0	0.21	--
3	Upright	3.40	104.2	0.32	--
3	Inverted	3.40	104.5	0.31	--
3	Upright	3.34	104.0	0.43	--
4	Inverted	3.32	103.0	0.41	--
5	Upright	3.33	103.6	0.56	--
5	Inverted	3.32	103.4	0.60	--
6	Upright	3.32	104.5	0.68	1579
6	Inverted	3.30	103.0	0.66	1709

Table 12

Formulation 4 at 40°C/75% RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.52	106.5	not detectable	1924
1	Upright	3.58	102.9	not quantifiable	1751
1	Inverted	3.57	103.6	not quantifiable	1755
2	Upright	3.49	102.5	0.35	--
2	Inverted	3.48	102.7	0.33	--
3	Upright	3.44	103.5	0.50	--
3	Inverted	3.44	103.5	0.48	--
6	Upright	3.39	101.5	1.00	1747
6	Inverted	3.39	101.4	0.99	1701

Table 13

Formulation 2 at 30°C/60% RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.64	104.0	not detectable	1711
1	Upright	3.60	101.5	not detectable	--
1	Inverted	3.59	100.5	not detectable	--
2	Upright	3.63	100.7	not detectable	--
2	Inverted	3.66	101.7	not detectable	--
3	Upright	3.51	104.7	not quantifiable	1665
3	Inverted	3.52	104.3	not quantifiable	1637
6	Upright	3.34	105.4	not quantifiable	1633
6	Inverted	3.40	104.2	not quantifiable	1595

Table 14

Formulation 3 at 30°C/60% RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.50	103.1	not detectable	1705
1	Upright	3.60	104.4	not detectable	1693
1	Inverted	3.60	104.4	not detectable	1884
2	Upright	3.50	104.0	not quantifiable	--
2	Inverted	3.50	103.1	not quantifiable	--
3	Upright	3.50	105.3	not quantifiable	--
3	Inverted	3.50	104.5	not quantifiable	--
6	Upright	3.46	104.7	0.68	1610
6	Inverted	3.45	104.3	0.66	1618

Table 15

Formulation 4 at 30°C/60% RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.52	106.5	not detectable	1924
1	Upright	3.57	104.6	not quantifiable	--
1	Inverted	3.59	103.8	not quantifiable	--
2	Upright	3.52	103.0	not quantifiable	--
2	Inverted	3.51	103.7	not quantifiable	--
3	Upright	3.48	104.5	not quantifiable	1810
3	Inverted	3.50	104.8	not quantifiable	1776
6	Upright	3.46	103.3	0.35	1770
6	Inverted	3.46	103.7	0.35	1709

Table 16

Formulation 2 at 25°C/60%RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.64	104.0	not detectable	1711
3	Upright	3.55	104.4	not detectable	--
3	Inverted	3.56	103.8	not detectable	--
6	Upright	3.46	104.0	not quantifiable	1640
6	Inverted	3.47	104.6	not quantifiable	1640

Table 17

Formulation 3 at 25°C/60%RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.50	103.1	not detectable	1705
3	Upright	3.50	104.8	not quantifiable	--
3	Inverted	3.50	104.3	not quantifiable	--
6	Upright	3.50	104.8	not quantifiable	1633
6	Inverted	3.42	104.4	not quantifiable	1938

Table 18

Formulation 4 at 25°C/60%RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.52	106.5	not detectable	1924
3	Upright	3.51	104.3	not quantifiable	--
3	Inverted	3.50	103.4	not quantifiable	--
6	Upright	3.47	103.7	0.24	1770
6	Inverted	3.48	103.7	0.24	1701

Table 19

Formulation 2 at 15°C/40%RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.64	104.0	not detectable	1711
3	Upright	3.62	103.2	not detectable	--
3	Inverted	3.62	103.4	not detectable	--
6	Upright	3.56	104.2	not detectable	1709
6	Inverted	3.55	104.1	not detectable	1839

Table 20

Formulation 3 at 15°C/40%RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.50	103.1	not detectable	1705
3	Upright	3.50	103.4	not detectable	--
3	Inverted	3.50	104.7	not detectable	--
6	Upright	3.51	104.1	not quantifiable	1701
6	Inverted	3.49	104.8	not quantifiable	1686

Table 21

Formulation 4 at 15°C/40%RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.52	106.5	not detectable	1924
3	Upright	3.51	105.5	not detectable	--
3	Inverted	3.52	105.6	not detectable	--
6	Upright	3.49	104.5	not quantifiable	1846
6	Inverted	3.49	104.0	not quantifiable	1801

Tables 10-21 above demonstrate that Formulations 2 - 4 according to the present invention remain both chemically and physically stable when stored at varying conditions of temperature and humidity as measured by scopolamine HBr content, degradation product and viscosity. Each of these parameters remained within acceptable limits as recognized by one skilled in the art even after 6 months of storage. The data indicate, however, that at PVA concentrations at about 100 mM (Formulation 4) the degradation product as represented by the % tropic acid is at 1.00% and 0.99% after 6 months of storage (Table 12). Thus, the 100 mM formulation (Formulation 4) approached

unacceptable levels representing chemical instability thereof at elevated temperatures for prolonged storage periods. Thus, the data suggest that nasal formulations at PVA concentrations above 100 mM are not likely to be useful due to chemical instability.

EXAMPLE 4

Stability of PVA Formulations at Different Buffer Concentrations

Example 4 is a direct comparison of the effect of the buffer concentration on the PVA Formulations (Formulations 2, 3 and 4) at 40°C/75%RH. This data is set forth in Table 22 and graphed in Figure 2, which demonstrates product degradation as a function of the percentage of tropic acid in the formulation over time.

Table 22

Effect of Buffer Concentration on Stability of PVA Formulations

Formulation #	Buffer Molarity (mM)	Tropic Acid (% LC) (ND=not detectable; NQ=not quantifiable)						
		Initial	1 month	2 month	3 month	4 month	5 month	6 month
2	20	ND	NQ	NQ	0.21	0.27	0.33	0.50
3	50	ND	NQ	0.22	0.32	0.43	0.56	0.68
4	100	ND	0.20	0.35	0.50	--	--	1.00

As is evident from Table 22 and Figure 2, Formulations 2, 3 and 4 prepared according to the present invention with PVA remain physically and chemically stable for up to 6 months. In fact, the formulations at 20 mM and 50 mM, as represented in Tables 10 and 11, respectively, provide excellent stability results even at the 6 month storage time, while Formulation 4 (100 mM) as represented by Table 12, approaches unstable limits of 1.00 % tropic acid, representing chemical degradation at the 6 month storage date. Moreover, it can be recognized from these data that formulations incorporating PVA prepared at a pH of about 3.5 and at concentrations above 100 mM lose chemical stability during storage.

Example 5

Comparison of Stability of Methyl Cellulose vs. PVA Formulations as a Function of Viscosity

Example 5 is a direct comparison of Formulation 1 (methyl cellulose) and Formulation 2 (PVA) at 40°C/75%RH highlighting the viscosity data as set forth in Table 23 below.

Table 23

Methyl Cellulose vs. PVA Formulations as a Function of Viscosity

Formulation #	Viscosity (cts)		
	Initial	1 month	6 month
1	4393	1452	206
2	1711	1714	1564

As is evident from a review of the results of Table 23, the nasal gel formulation prepared according to the present invention with polyvinyl alcohol as a gelling agent in a formulation at about pH 3.5 and concentration of 20 mM (Formulation 2) maintains a substantially constant viscosity over time, thus evidencing that such formulations remain chemically and physically stable for periods of 6 months. The nasal gel formulation prepared with methyl cellulose as a gelling agent in a formulation at about pH 3.5 and concentration of 25 mM (Formulation 1) demonstrates a significant decrease in viscosity after only one month of storage, with a remarkable decrease after 6 months of storage, thus evidencing that such a formulation is chemically and physically unstable.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.

WHAT IS CLAIMED IS:

1. An intranasal formulation comprising scopolamine in a pharmaceutically acceptable carrier at a pH below about 4.0 and a buffer salt concentration below about 200 mM, said carrier incorporating polyvinyl alcohol.

2. An intranasal formulation as in claim 1, wherein said carrier is a pharmaceutically acceptable gel.

3. An intranasal formulation as in claim 1, wherein said polyvinyl alcohol is combined with one or more additional gelling agents or bio-adhesives selected from the group including alginates, gums, starches, polyacrylates, dextrans, chitosans and mixtures thereof.

4. An intranasal formulation as in claim 1, wherein said concentration is at or below about 100 mM.

5. An intranasal formulation as in claim 1, wherein said concentration is at or below about 50 mM.

6. An intranasal formulation as in claim 1, wherein said pH is about 3.5.

7. An intranasal formulation as in claim 1, wherein said scopolamine is provided as a chemically modified equivalent or pharmaceutically acceptable salt thereof.

8. An intranasal formulation as in claim 7, wherein said scopolamine is provided as scopolamine hydrobromide.

9. An intranasal formulation for preventing and/or treating nausea and/or vomiting described in claim 1.

10. An intranasal formulation as in claim 1 further including buffering agents, thickening agents, tolerance enhancers, surfactants, excipients, preservatives and combinations thereof.

11. An intranasal gel formulation for preventing and/or treating motion sickness comprising scopolamine hydrobromide in a gel solution at or below a pH at about 3.5 and a buffer salt concentration at or below about 100 mM, said gel solution incorporating polyvinyl alcohol as a gelling agent.

12. An intranasal formulation as in claim 11, wherein said gel solution further includes gelling agents and/or bio-adhesives selected from the group including alginates, gums, starches, polyacrylates, dextrans, chitosans and mixtures thereof.

13. An intranasal gel formulation as in claim 11 further including buffering agents, thickening agents, tolerance enhancers, surfactants, excipients, preservatives and combinations thereof.

14. A method of preventing and/or treating nausea and/or vomiting comprising administering intranasally to a mammal an effective amount of scopolamine, chemically modified equivalents and pharmaceutical salts thereof in a pharmaceutically acceptable carrier at a pH below about 4.0 and a buffer salt concentration below about 200 mM, said carrier incorporating polyvinyl alcohol.

15. A method as in claim 14, wherein said carrier further includes gelling agents and/or bio-adhesives selected from the group including alginates, gums, starches, polyacrylates, dextrans, chitosans and mixtures thereof.

16. A method as in claim 14, wherein said carrier is a gel for intranasal administration.

17. A method as in claim 14, wherein said salt concentration is at or below about 100 mM.

18. A method as in claim 14, wherein said salt concentration is at or below about 50 mM.

19. A method as in claim 14, wherein said pH is about 3.5.

20. A method as in claim 14, wherein said scopolamine is provided as scopolamine hydrobromide.

21. A method as in claim 14, wherein a nausea and/or vomiting preventing or treating scopolamine free base plasma concentration is achieved within about 5 minutes.

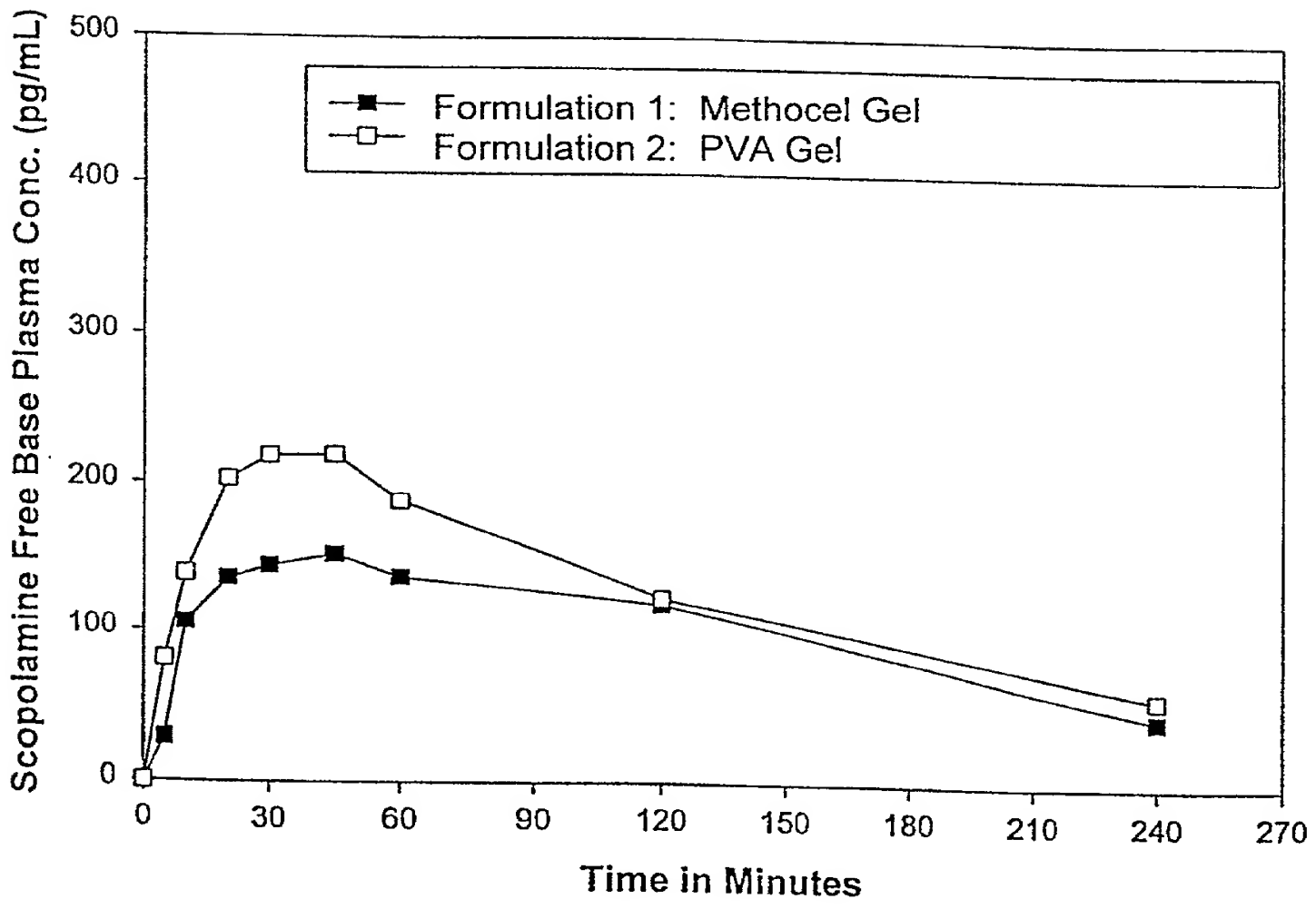
Formulation 1: Methocel Gel
Formulation 2: PVA Gel
Scopolamine Free Base Plasma Conc. (pg/mL)
500
400
300
200
100
0
0
30
60
90
120
150
180
210
240
270
Time in Minutes

Fig. 1

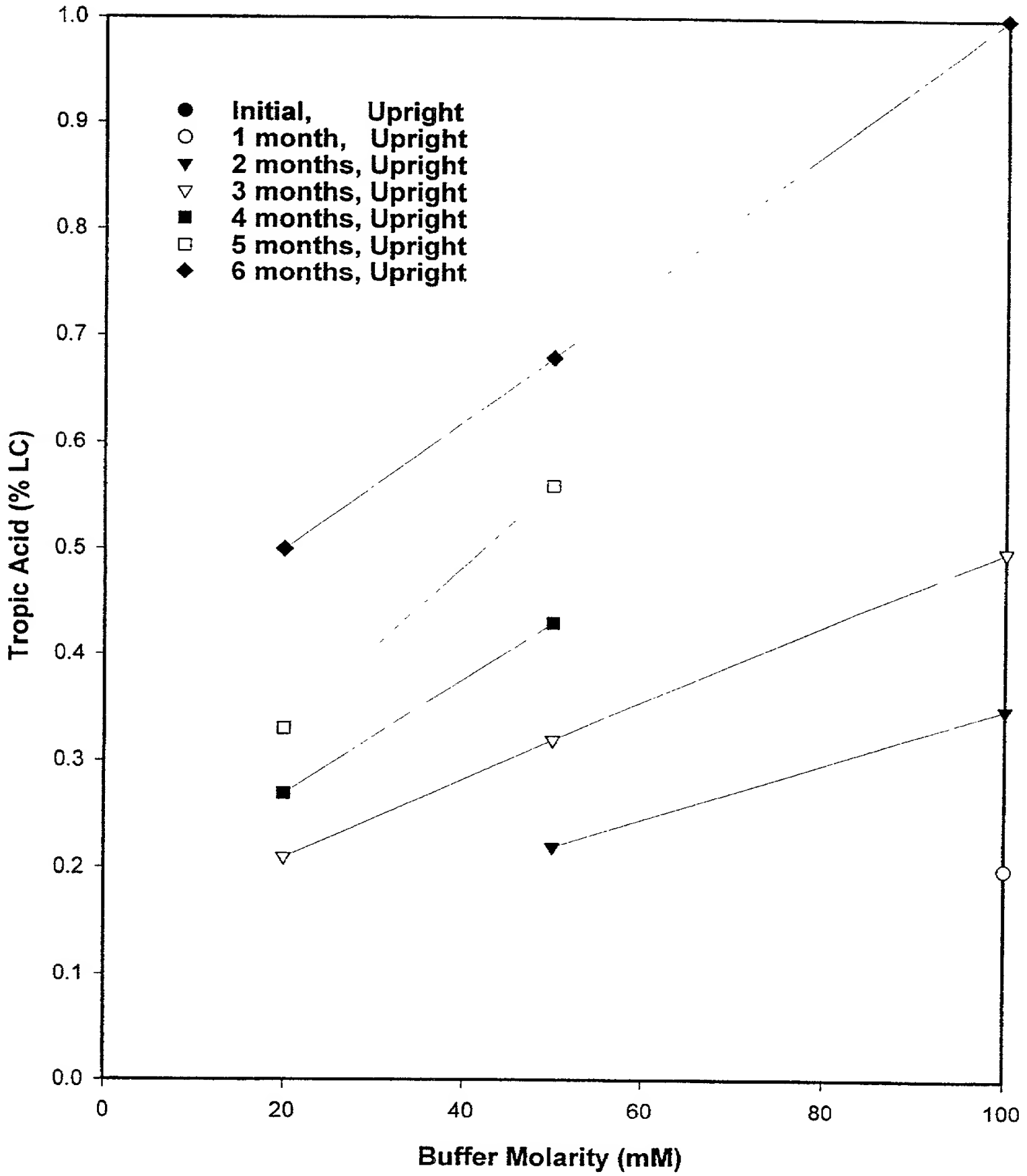
Initial, Upright
1 month, Upright
2 months, Upright
3 months, Upright
4 months, Upright
5 months, Upright
6 months, Upright
Tropic Acid (% LC)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
20
40
60
80
100
Buffer Molarity (mM)

Fig. 2

Attorney's Docket No. 719-75 PCT

PATENT

COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL, CONTINUATION OR CIP)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type: *(check one)*

[X] Original
[ ] Supplemental
[ ] Design

[] National Stage PCT
[ ] Divisional
[ ] Continuation
[ ] Continuation-in-Part (CIP)

INVENTORSHIP IDENTIFICATION

NOTE: If the inventors are each not the inventors of all the claims an explanation of the facts, including the ownership of all the claims at the time the last claimed invention was made, should be submitted.

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

INTRANASAL FORMULATIONS CONTAINING SCOPOLAMINE AND METHOD OF TREATING MOTION SICKNESS

the specification of which: *(complete (a), (b) or (c))*

(a) [ ] is attached hereto.

(b) [ ] was filed on _____ as
[ ] Serial No. _____ or
[ ] Express Mail No. _____, as Serial No. not yet known
and was amended on _____. *(If applicable)*

(c) [X] was described and claimed in PCT International Application No. PCT/ (FILED HEREWITH)
filed on _____ and as amended under PCT Article 19 on _____. *(If any)*

ACKNOWLEDGMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above, and that the filing of said specification, if heretofore filed, was authorized by me.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

CLAIM OF PRIORITY OF EARLIER FOREIGN APPLICATION(S) UNDER 35 U.S.C. §119(a)-(d)

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

(List prior foreign/PCT application(s) filed within 12 months (6 months for design) prior to this U.S. application.)

NOTE. Where item (c) is entered above and the International Application which designated the U.S. claimed priority check item (e), enter the details below and make the priority claim.

COUNTRY (or PCT)	APPLICATION NO.	DATE OF FILING *(Day/Month/Year)*	PRIORITY CLAIMED UNDER 35 USC §119
			[ ]YES [ ]NO
			[ ]YES [ ]NO

CLAIM FOR BENEFIT OF PRIOR U.S. PROVISIONAL APPLICATION(S) UNDER 35 U.S.C. §119(e)

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

(List prior U.S. provisional applications.)

PROVISIONAL APPLICATION NO.	FILING DATE *(Day/Month/Year)*
60/058,651	11 September 1997

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S) UNDER 35 U.S.C. 120

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in such prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

(List prior U.S. applications or PCT international applications designating the U.S. for benefit under 35 U.S.C. §120.)

U.S. APPLICATIONS		**STATUS** *(Check One)*		
U.S. SERIAL NO.	U.S. FILING DATE *(Day/Month/Year)*	Patented	Pending	Abandoned
0 /		[]	[]	[]
0 /		[]	[]	[]

PCT APPLICATIONS DESIGNATING THE U.S.			**STATUS** *(Check One)*		
PCT APPLN. NO.	PCT FILING DATE *(Day/Month/Year)*	U.S. SERIAL NOS. ASSIGNED (If any)	Patented	Pending	Abandoned
PCT/			[]	[]	[]
PCT/			[]	[]	[]

35 USC 119 PRIORITY CLAIM, IF ANY, FOR ABOVE LISTED U.S./PCT APPLICATIONS

PRIORITY APPLICATION NO.	PRIORITY COUNTRY	FILING DATE *(Day/Month/Year)*	ISSUE DATE *(Day/Month/Year)*

POWER OF ATTORNEY

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office in connection therewith:

Charles R. Hoffmann, Reg. No. 24,102; Ronald J. Baron, Reg. No. 29,281; Gerald T. Bodner, Reg. No. 30,449; Alan M. Sack, Reg. No. 31,874; A. Thomas Kammer, Reg. No. 28,226; Arlene D. Morris, Reg. No. 32,657; R. Glenn Schroeder, Reg. No. 34,720; Glenn T. Henneberger, Reg. No. 36,074; Livia Boyadjian, Reg. No. 34,781; Jessica H. Tran, Reg. No. 40,842; Irving N. Feit, Reg. No. 28,601; Anthony E. Bennett, Reg. No. 40,910; Gregory A. Bachmann, Reg. No. P41,593; Steven T. Zuschlag, Reg. No. P43,309, Susan A. Sipos, Reg. No. P43,128; William D. Schmidt, Reg. No. 39,492; and Kevin E. McDermott each of them of HOFFMANN & BARON, 350 Jericho Turnpike, Jericho, New York 11753; and Daniel A. Scola, Jr., Reg. No. 29,855; Salvatore J. Abbruzzese, Reg. No. 30,152; Kirk M. Miles, Reg. No. 37,891; Kevin C. Hooper, Reg. No. 40,402; and Robert F. Chisholm, Reg. No. 39,939, each of them of HOFFMANN & BARON, 1055 Parsippany Boulevard, Parsippany, New Jersey 07054.

PLEASE SEND CORRESPONDENCE TO:

HOFFMANN & BARON
350 Jericho Turnpike
Jericho, NY 11753

PLEASE DIRECT TELEPHONE CALLS TO:

Attorney:
Kirk M. Miles
(973) 331-1700

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

1 - CO

Full name of sole or first inventor:	Achari, Raja G.
Country of Citizenship:	USA
Residence Address:	52 Indian Run, Millington, NJ 07946
Post Office Address:	**Same as Above**

Date: 9-10-98 Inventor's signature Raja Achari

2 - CO

Full name of second joint inventor:	Behl, Charanjit R.
Country of Citizenship:	USA
Residence Address:	658 Veterans Memorial Highway, #1A, Hauppauge, NY 11788
Post Office Address:	**Same as Above**

Date: 9-10-98 Inventor's signature Charanjit R. Behl.

3 - CO

Full name of third joint inventor:	Chowhan, Prafulla K.
Country of Citizenship:	USA
Residence Address:	74 Sampson Avnue, Ronkonkoma, NY 11779
Post Office Address:	**Same as Above**

Date: 9-10-98 Inventor's signature Prafulla Chowhan

(7)
OVER

4 - 00

Full name of fourth joint inventor: deMeireles, Jorge C.

Country of Citizenship: Portugal

Residence Address: 33 Renee Road, Syosset, NY 11791

Post Office Address: **Same as Above**

Date: 9/10/98 Inventor's signature

5 - 00

Full name of fifth joint inventor: Dua, Ramneik

Country of Citizenship: India

Residence Address: 173 Hawthorne Avenue, Apt. 172, Central Islip, NY 11722

Post Office Address: **Same as Above**

Date: 9/10/98 Inventor's signature

6 - 00

Full name of sixth joint inventor: Romeo, Vincent D.

Country of Citizenship: USA

Residence Address: 104 Harbor Lane, Massapequa, NY 11762

Post Office Address: **Same as Above**

Date: 9/10/98 Inventor's signature

7 - 00

Full name of seventh joint inventor: Sileno, Anthony P.

Country of Citizenship: USA

Residence Address: 10 Highview Boulevard, Brookhaven Hamlet, NY 11719

Post Office Address: **Same as Above**

Date: 9/10/98 Inventor's signature